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REMARKS

Applicants have amended claims 19 and 37 in response to the Examiner's recommendation at page 5 of the Office Action to expedite prosecution and to make explicit that which was implicit, namely that the surface modified powder is prepared in the absence of any solvent. This amendment is supported by the original claims, as well as pages 6 – 8 of the specification. Claim 32 has been amended to correct a minor typographical error. As such, these amendments do not introduce any new matter and their entry is respectfully requested.

Claims 19 – 46 were rejected under 35 USC § 103(a) as being unpatentable over GB 1,480,175.

The present invention is directed to a surface modified powder, which is obtained by thoroughly blending an active agent with a surface modifying material, without the use of a solvent such as water. The flowability of the obtained surface modified powder becomes at most 42° when measured by the angle of repose. Applicants discovered that high flowability can be achieved **without the use of any solvent such as water**. The resultant surface modified powder enables direct tableting and provides a material to prepare an excellent fast disintegrating tablet. This property of fast disintegration at the appropriate time is very desirable. The excellent properties of such tablets is further described in the applicants' article attached hereto (Kato et al., *J. Pharm. Sci. Technol., Jpn.* 62:87-94 (2002)).

Flow properties of solid pharmaceutical compositions are usually determined by measuring the angle of repose. Anyone skilled in the art would readily appreciate that an angle of repose of at most at 42° is an indication of a highly flowable material.

In contrast, GB 1,480,175 (the '175) describes coated tablets where the pharmacologically active agent must be mixed with maltose, as claimed for example in claim 1. The '175 is restricted to direct compression of the maltose-containing mixture into a tablet. The novel aspect of the '175 is the use of maltose; nothing teaches or suggests a preparing a fast-disintegrating tablet in the absence of a solvent, let alone a powder having a flowability of at most 42° in terms of an angle of repose. Thus, the '175 in no way makes it obvious to exclude the use of a solvent in preparing a fast-disintegrating tablet. Accordingly, applicants respectfully request that the rejection under 35 USC § 103 (a) over GB 1,480,175 be withdrawn.

Claims 19 – 46 were rejected under 35 USC § 103(a) as being unpatentable over JP 10114655 (abstract).

Nothing in JP 10114655 teaches or suggests that its process for preparing a fast disintegrating tablet could be performed in the absence of a solvent, in contrast to the claimed invention. JP 10114655 teaches no more than a conventional method for formulating a solid pharmaceutical preparation, wherein water is used as a solvent to prepare a granulated product. Indeed, all of the Examples describe a conventional manner for formulating a tablet by mixing and granulating the medicine, additive and disintegrating agent in the presence of water in a mixing granulator and compressing the granulated product to formulate the tablet.

Similarly, unlike the powder of the present invention, it would not have a flowability as required by the claims. Therefore, JP 10114655 neither teaches nor suggests the surface modified powder of the present invention which is prepared without the use of any solvent such as water. Therefore, applicants respectfully request that the rejection under 35 USC § 103 (a) over JP 10114655 be withdrawn.

In view of the foregoing, applicant respectfully submits that all claims comply with 35

• Application No. 09/936,558
Amendment dated December 29, 2003
Reply to Office Action of July 28, 2003

U.S.C. § 103(a) and are in condition for allowance. Early and favorable action is requested.

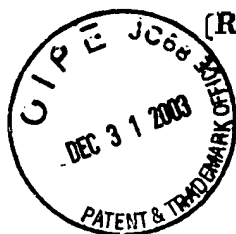
In the event that any additional fee is required, please charge Deposit Account No. 50-0850.

Respectfully submitted,

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[Regular Article]

Rapidly Disintegrating Tablets Prepared by a Surface-Modifying Method — Comparison of Disintegrants —

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Summary: We examined the physical properties of tablets prepared by the direct compression of a mixture of surface-modified ibuprofen with light anhydrous silicic acid (200FAD) by the method established in our previous paper (Y. Kato, *et al.*, *J. Pharm. Sci. Technol., Jpn.*, 61 (3), 109-118 (2001)), a disintegrant, and other excipients. The disintegrants were chosen from derivatives of starch, of a synthetic polymer of polyvinylpyrrolidone, and of cellulose. The disintegration mechanism, disintegration time, and hardness of tablets were greatly affected by the kind and amount of disintegrant, the physical properties of the drug, and the formulation. The effect of compression force differed with the kind of disintegrant. Tablets containing some disintegrant swelled under humidity when stored in a nonpackaged state. Therefore it was found that rapidly disintegrating tablets could be designed to suit the needs of individual patients to improve compliance, by a choice of a suitable disintegrant for the properties of the desired tablets or by a combination of disintegrants with different properties.

Keywords: surface modifying; disintegrant; direct compression; ibuprofen

Introduction

Drugs that are easy to swallow by elderly and pediatric patients have recently been diligently studied.¹⁻⁶⁾ Rapidly disintegrating tablets that break up in the oral cavity when taken with water do not lodge in the throat. We believed that drugs in the form of rapidly disintegrating tablets could be administered with a glass of water (180-200 mL)^{7,8)} at medical facilities. This would consequently improve compliance. In a previous paper,⁹⁾ we revealed our finding that the flowability of ibuprofen, used as a model drug having strong adhesive-agglomerative properties, was improved by a surface-modifying method implementing a high-speed agitating granulator typically used for wet granulation.

Furthermore, we found that rapidly disintegrating tablets could be prepared by the direct compression of a mixture of surface-modified ibuprofen and additives such as disintegrants. In this study, we prepared rapidly disintegrating tablets by changing the kind and amount of disintegrant and evaluated their properties to decide on suitable disintegrants.

Experimental

1. Materials

As in our previous paper,⁹⁾ ibuprofen (IP : BASF) was chosen as a model drug. Light anhydrous silicic acid (200FAD : Nippon Aerosil Co., Ltd.) was used as a surface-modifying agent. Partly pregelatinized starch (PCS : Asahi Kasei Co., Ltd.), crospovidone

TABLE I. Disintegrants Used in This Study

Disintegrant	Grade	
Partly Pregelatinized Starch (PCS)	JPE 1998	Asahi Kasei Co., Ltd.
Crospovidone (Polyplasdone XL)	JPE 1998	ISP Japan Co., Ltd.
Low Substituted Hydroxypropylcellulose (L-HPC11)	JP 14	Shin-Etsu Chemical Industries Co., Ltd.
Carmellose (NS-300)	JP14	Gotoku Chemical Co., Ltd.
Carmellose Calcium (ECG-505)	JP14	Gotoku Chemical Co., Ltd.
Croscarmellose Sodium (Ac-Di-Sol)	JPE 1998	Asahi Kasei Co., Ltd.

(Polyplasdone XL : ISP Japan Co., Ltd.), low substituted hydroxypropylcellulose (L-HPC11 : Shin-Etsu Chemical Industries Co., Ltd.), carmellose (NS-300 : Gotoku Chemical Co., Ltd.), carmellose calcium (ECG-505 : Gotoku Chemical Co., Ltd.) and croscarmellose sodium (Ac-Di-Sol : Asahi Kasei Co., Ltd.) were used as disintegrants and are shown in Table I. Crystalline cellulose (Ceolus : Asahi Kasei Co., Ltd.) was used as a basic excipient. Magnesium stearate (Kyoudo Yakuhin Co., Ltd.) was used as a lubricant.

2. Surface modification of ibuprofen

IP was surface-modified by the method established in our previous paper⁹⁾ by use of a high-speed agitating granulator (Laboratory Matrix LMA-10 : Nara Machinery Co., Ltd.). Light anhydrous silicic acid was chosen as the surface-modifying agent because it strongly improved the flowability of IP in the previous study⁹⁾ and was added at 2% to IP.

3. Comparison of the disintegrants

We measured the physical properties of both disintegrants and tablets to investigate the properties of disintegrants and the mechanism of disintegration.

4. Preparation of tablets

Surface-modified IP and additives such as disintegrants were blended in a V-type mixer (V-10 : Tokuju Co., Ltd.) for 5 min. Flat-faced tablets weighing 300 mg and measuring 10 mm in diameter, were prepared with a rotary tableting machine (HT-AP15SS II : Hata Iron Works). The weight, thickness, hardness, disintegration time, and wetting time of each tablet were measured. The formulations of tablets are shown in Table II, and the preparation method is shown in Table III.

5. Measurement of disintegration time

The disintegration time of tablets was measured by the same two methods used in the previous paper,⁹⁾ disintegration time (1) and disintegration time (2).

6. Measurement of wetting time

Wetting time was measured by the previous method,⁹⁾ which was established by Bi *et al.*¹⁰⁾

Results and Discussion

1. Comparison of disintegrants

In general, the disintegrant is added in a relatively large amount compared with other additives, and the particle shape, particle diameter, and disintegration mechanism vary with the kind of disintegrant.¹¹⁾

Besides PCS, a starch derivative used in the previous paper,⁹⁾ Polyplasdone XL, which is a synthetic polymer of polyvinylpyrrolidone derivatives, and L-HPC11, NS-300, ECG-

TABLE II. Formula for Rapidly Disintegrating Tablets (300 mg/tab) (mg)

Materials	Formula No.									
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6	No. 7	No. 8	No. 9	No. 10
Ibuprofen ^{a)}					51.0					
PCS	60.0	—	—	—	—	—	90.0	120.0	60.0	45.0
Polyplasdone XL	—	60.0	—	—	—	—	—	—	30.0	45.0
L-HPC11	—	—	60.0	—	—	—	—	—	—	—
NS-300	—	—	—	60.0	—	—	—	—	—	—
ECG-505	—	—	—	—	60.0	—	—	—	—	—
Ac-Di-Sol	—	—	—	—	—	15.0	—	—	—	—
Crystalline cellulose	120.0	120.0	120.0	120.0	120.0	165.0	90.0	60.0	90.0	90.0
Sweetening agent and corrigent					60.0					
Magnesium stearate					9.0					

a) Surface modified with 2% light anhydrous silicic acid.

TABLE III. Operating Conditions and Flow Diagram for the Preparation of Rapidly Disintegrating Tablets

<Surface modification>	
Machine: High-speed agitating granulator (Laboratory Matrix LMA-10: Nara Machinery Co., Ltd.)	
Ibuprofen (500 g) and light anhydrous silicic acid (10 g)	
↓	
Surface modification (25 min)	
Revolution of blade : 300 min ⁻¹	
Revolution of chopper : 1,500 min ⁻¹	
<Mixing>	
Machine : V-type mixer (V-10 : Tokuju Co., Ltd.)	
Ibuprofen (surface modified) and additives (total : 1 kg)	
↓	
Mixing (40 min ⁻¹ , 5 min)	
<Tableting>	
Machine : Rotary tableting machine (HT-AP16SS II : Hata Iron Works)	
300 mg/tab, 10 mmφ (flat face)	

505, and Ac-Di-Sol, which are cellulose derivatives, were used as disintegrants in this study.

We measured the physical properties of disintegrants and the tablets prepared with each. Flat-faced tablets weighing 200 mg and measuring 10 mm in diameter were prepared with a rotary tableting machine at a compression force of 62.4 MPa. The physical properties of the disintegrants and tablets are shown in Tables IV and V. The hardness and disintegration time of the tablets differed with the kind of disintegrant. Some tablets disintegrated rapidly, but some hardly disintegrated at all.

The tablets were prepared by the use of surface modified IP with 2% light anhydrous silicic acid by the method shown in Table III, based on formulations shown in Table II. The physical properties of the tablets are listed in Table VI.

The tablet consisting only PCS, which is a starch derivative, had the slowest disintegration time and the greatest hardness value. But the disintegration time (1) of the tablet formulated with PCS as a disintegrant (No. 1) was within 30 sec, and the hardness was 36.9 N. The tablet with Polyplasdone XL as a disintegrant (No. 2), which is a synthetic polymer of polyvinylpyrrolidone derivatives, disintegrated rapidly and had a hardness of 51.2 N. Tablets formulated with cellulose derivatives (No. 3 to No. 6) had a higher hardness value and showed good compressibility, but their disintegration time (1) exceeded 30 sec. The tablet containing NS-300 alone disintegrated rapidly, but the tablet with NS-300 as a disintegrant (No. 4) broke apart slower than tablets with other disinte-

TABLE IV. Physical Properties of Disintegrants

	PCS	Polyplasdone XL	L-HPC11	NS-300	ECG-505	Ac-Di-Sol
Angle of repose (°)	48	48	51	52	51	53
Aerated bulk density (g/mL)	0.52	0.24	0.31	0.28	0.40	0.35
Packed bulk density (g/mL)	0.71	0.31	0.54	0.46	0.62	0.65

TABLE V. Physical Properties of Tablets of Disintegrants (compression force: 62.4 MPa)

	PCS	Polyplasdone XL	L-HPC11	NS-300	ECG-505	Ac-Di-Sol
Thickness (mm)	2.55	2.98	2.40	2.94	2.58	2.40
Hardness (N)	10.3	128.7	89.2	24.3	31.9	54.1
Disintegration time (1)(sec)	767.0	20.0	320.7	15.0	161.7	210.0

TABLE VI. Physical Properties of Rapidly Disintegrating Tablets (1)
(compression force: 87.4 MPa)

	Formula No.					
	No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
Weight (mg/tab)	300.5	299.8	300.8	300.5	300.0	300.8
Thickness (mm)	3.46	3.46	3.34	3.50	3.32	3.27
Hardness (N)	36.9	51.2	66.8	39.5	55.3	79.0
Friability (%)	1.46	0.48	0.68	1.78	1.16	0.53
Disintegration time (1)(sec)	28.5	11.4	48.9	95.4	51.8	45.3
Disintegration time (2)(sec)	54.8	25.8	77.5	— ^a	85.1	— ^a
Wetting time (sec)	58.9	11.8	70.1	33.1	79.3	38.1

^a) Had not disintegrated after 120 sec.

grants did. Tablets formulated with NS-300 or Ac-Di-Sol (Nos. 4 and 6) swelled in water, but had not disintegrated after 120 sec in the disintegration test (2). It was presumed that the stress on tablets in the disintegration test (1) could not be applied in test (2).

Tablets (Nos. 1 and 6) were prepared at a compression force of 87.4 MPa, and the disintegration behavior of each tablet in water was then observed at regular intervals. As shown by the photographs in Fig. 1, tablets formulated of PCS, Polyplasdone XL or L-HPC11 (Nos. 1 and 3) disintegrated while swelling in water (disintegrate-swell type: Dis-Sw type), but tablets formulated of NS-300 or Ac-Di-Sol (Nos. 4 and 6) swelled without disintegrating (swell type: Sw type), and those formulated with ECG-505 (No. 5) disintegrated without swelling (disintegrate type: Dis type). The mechanism of disintegration differed with the kind of disintegrant used, and disintegrants could be classified into two groups, having a strong ability to disintegrate or to swell. Rapidly disintegrating tablets need to disintegrate immediately on coming into contact with water. Therefore Dis-Sw and Dis types of disintegrants are suitable. However, tablets formulated with L-HPC11 or ECG-505 disintegrated slower than those with PCS or Polyplasdone XL. It was found that the mechanism of disintegration and the physical properties of tablets, consisting of a single disintegrant prepared as described above, differed from those of rapidly disintegrating tablets and were influenced by the physical properties of the active ingredient and the formulation of the tablet.

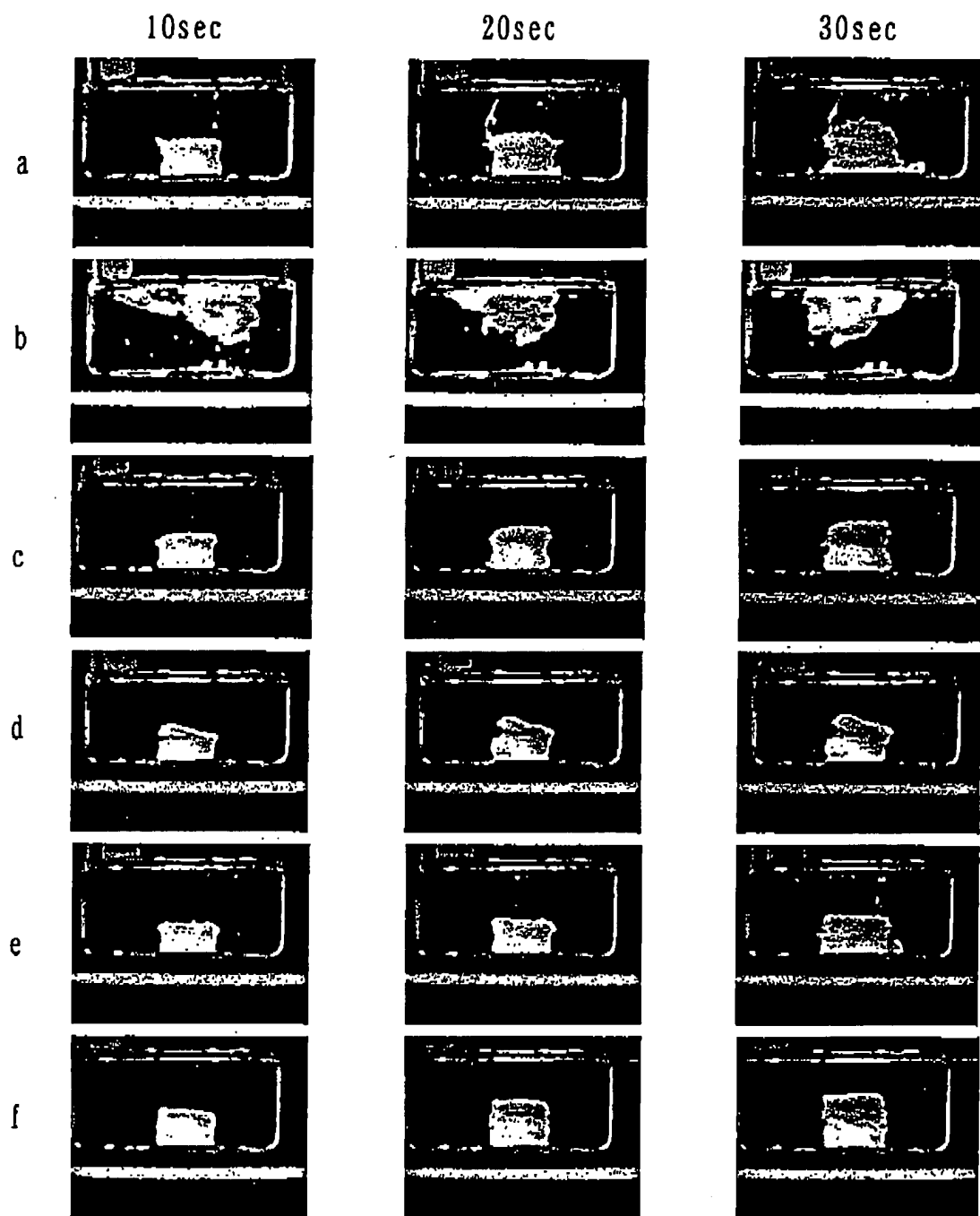


Fig. 1. Disintegrating Properties of Tablets (compression force : 87.4 MPa)

- a: Formulated with PCS (No. 1).
- b: Formulated with Polyplasdone XL (No. 2).
- c: Formulated with L-HPC11 (No. 3).
- d: Formulated with NS-300 (No. 4).
- e: Formulated with ECG-505 (No. 5).
- f: Formulated with Ac-Di-Sol (No. 6).

2. Effect of compression force

For formulations Nos. 3 and 6, the disintegration time (1) of tablets prepared at 87.4 MPa exceeded 30 sec. Thus the tablets were prepared at a lower compression force (62.4 MPa). The physical properties of the tablets are shown in Table VII. In the formulation containing L-HPC11 or ECG-505 (Nos. 3 and 5), tablets prepared at 62.4 MPa disintegrated in 30 sec and had a hardness of 49.6 N and 38.4 N, respectively. Compared with No. 3 and No. 5, the hardness of the tablet prepared with NS-300 (No. 4) at 62.4 MPa was greater, but the disintegration was slower.

For the formulation with PCS and Polypladsone XL (Nos. 1 and 2), the disintegration time (1) of the tablet prepared at 87.4 MPa was less than 30 sec. Thus the tablets were prepared at a higher compression force (124.9 MPa). The physical properties of the tablets are shown in Table VII. In the formulation containing PCS (No. 1), the disintegration time and the hardness increased with increasing compression force. In the formulation with Polypladsone XL (No. 2), the disintegration time was influenced little by compression force, but the hardness rose as the force increased.

The influence of compression force on tablet hardness was remarkable in the formulation containing Polypladsone XL.

3. Effect of humidity

Tablets were prepared with formulations Nos. 1 and 6 as shown in Table IV, and stored at 25°C, 75% RH. The diameter and thickness of these tablets measured at regular intervals are shown in Table VIII.

Compared with other tablets, the tablet formulated with Polypladsone XL (No. 2) swelled under the humidity. Tablets would swell when prepared with formulation No. 2 as a nonpackaged form. Stored forms and stability are to be taken into consideration in product design. Notably, if Polypladsone XL is to be used in rapidly disintegrating tablets, the amount added must be decreased.

4. Comparison of added amounts of disintegrants

Tablets were prepared with various amounts of PCS because those prepared with formulation No. 1 at a compression force of 87.4 MPa showed a suitable hardness and a disintegration time (1) of less than 30 sec. As shown in Table IX (Nos. 1, 7 and 8), the disintegration time and wetting time of tablets prepared at 87.4 MPa were scarcely affected by the amount of PCS in the formulation. The hardness of the tablet was decreased and the amount of crystalline cellulose decreased as the amounts of PCS increased, the latter resulting in a reduction in compressibility. It was revealed that the disintegration time and the hardness of tablets were affected by the type of disintegrant. So the tablets were

Table VII. Physical Properties of Rapidly Disintegrating Tablets (2)

	Formula No.											
	No. 1		No. 2		No. 3		No. 4		No. 5		No. 6	
Compression force (MPa)	87.4	124.9	87.4	124.9	62.4	87.4	62.4	87.4	62.4	87.4	62.4	87.4
Weight (mg/tab)	300.5	300.1	299.8	300.6	299.1	300.8	300.4	300.5	299.5	300.0	300.3	300.8
Thickness (mm)	3.46	3.31	3.46	3.32	3.42	3.34	3.72	3.50	3.49	3.32	3.38	3.27
Hardness (N)	36.9	51.5	51.2	86.1	49.6	66.8	26.8	39.5	38.4	55.3	60.2	79.0
Friability (%)	1.46	0.86	0.48	0.42	1.04	0.68	3.53	1.78	1.91	1.16	0.88	0.53
Disintegration time (1)(sec)	28.5	57.0	11.4	13.2	22.1	48.9	60.5	95.4	25.7	51.8	34.9	45.3
Disintegration time (2)(sec)	54.8	133.6	25.8	27.1	32.5	77.5	— ^{a)}	— ^{a)}	54.6	85.1	— ^{a)}	— ^{a)}
Wetting time (sec)	58.9	78.4	11.8	20.5	40.2	70.1	23.2	33.1	54.4	79.3	25.3	38.1

a) Had not disintegrated after 120 sec.

TABLE VIII. Diameter and Thickness of Tablets Compressed at 87.4 MPa (stored at 25°C, 75%RH)

Storage time (hr)	Formula No.											
	No. 1		No. 2		No. 3		No. 4		No. 5		No. 6	
	D	T	D	T	D	T	D	T	D	T	D	T
0	10.05	3.33	10.18	3.68	10.00	3.34	10.05	3.32	10.00	3.20	9.99	3.20
1	10.09	3.45	10.40	4.03	10.07	3.40	10.18	3.45	10.11	3.32	10.04	3.33
3	10.24	3.52	10.57	4.24	10.11	3.44	10.20	3.52	10.10	3.37	10.10	3.35
5	10.25	3.52	10.65	4.37	10.13	3.50	10.19	3.54	10.12	3.40	10.11	3.35
15	10.25	3.59	10.74	4.59	10.16	3.57	10.24	3.61	10.16	3.46	10.12	3.43

D : Diameter of tablets (mm), T : Thickness of tablets (mm).

TABLE IX. Physical Properties of Rapidly Disintegrating Tablets (3) (compression force : 87.4 MPa)

	Formula No.			
	No. 7	No. 8	No. 9	No. 10
Weight (mg/tab)	299.4	300.7	300.1	299.7
Thickness (mm)	3.42	3.49	3.56	3.48
Hardness (N)	23.2	13.5	31.1	49.7
Disintegration time (1)(sec)	26.1	38.8	16.8	17.7
Disintegration time (2)(sec)	51.1	61.6	28.1	31.0
Wetting time (sec)	61.5	80.1	25.5	20.6

prepared at 87.4 MPa with both PCS and Polyplasdone XL, which exhibited good disintegration and compression-forming ability (Nos. 9 and 10), and the physical properties of the tablets were measured. The disintegration time and the wetting time of tablets decreased rapidly, and the hardness was increased with the addition of Polyplasdone XL, compared with the formulation containing only PCS (No.7).

We therefore prepared rapidly disintegrating tablets by using a Dis-Sw type of disintegrant or by combining Sw and Dis types. It was found that with the simultaneous addition of Polyplasdone XL or L-HPC11, both of which have good compressibility, the hardness of tablets increased, maintaining the rapid disintegration. Therefore rapidly disintegrating tablets could be designed with the consideration of patient needs.

Conclusions

We examined the physical properties of tablets prepared by the direct compression of a mixture of surface-modified ibuprofen with light anhydrous silicic acid (200FAD) by the method established in our previous paper,⁹⁾ a disintegrant, and other excipients. The disintegrants were chosen from derivatives of starch, of a synthetic polymer of polyvinylpyrrolidone, and of cellulose. The mechanism of disintegration, the disintegration time, and the hardness of tablets were greatly affected by the kind and amount of disintegrant, the physical properties of the drug, and the formulation. The effect of compression force differed with the type of disintegrant. Tablets containing some disintegrant swelled under humidity when stored in a nonpackaged state. Therefore it was found that rapidly disintegrating tablets could be designed to suit the needs of individual patients to improve compliance through a choice of a suitable disintegrant for the properties of the desired tablets or a combination of disintegrants with different properties. The optimization of a formulation for rapidly disintegrating tablets is our next aim, so we will investigate the relationship between the disintegrating and swelling mechanisms of disintegrants and the wetting properties of tablets.

References

- 1) A. Watanabe, T. Hanawa, M. Sugihara, New oral dosage form for the elderly -Rapid dissolving tablet in mouth without addition of water-, *J. Pharm. Sci. Technol., Jpn.*, **54** (2), 103-110 (1994).
- 2) T. Hanawa, A. Watanabe, T. Tsuchiya, R. Ikoma, M. Hidaka, M. Sugihara, New oral dosage form for elderly patients: Preparation and characterization of silk fibron gel, *Chem. Pharm. Bull.*, **43** (2), 284-288 (1995).
- 3) T. Hanawa, A. Watanabe, T. Tsuchiya, R. Ikoma, M. Hidaka, M. Sugihara, New oral dosage form for elderly patients. II. Release behavior of benfotiamine from silk fibron gel, *Chem. Pharm. Bull.*, **43** (5), 872-876 (1995).
- 4) Y. Bi, Y. Yonezawa, H. Sunada, Rapidly disintegrating tablet prepared by the wet compression method : mechanism and optimization, *J. Pharm. Sci.*, **88**, 1004-1010 (1999).
- 5) K. Masaki, The collected papers of the 22nd Conference on Pharmaceutical Technology, p. 79-84, July 1997, Kisarazu, Japan.
- 6) Y. Honda, M. Nakano, Evaluation of preference for swallowing orally disintegrating famotidine tablet in outpatients, *Jpn. J. Hosp. Pharm.*, **24** (5), 533-540 (1998).
- 7) T. Yadomae, KUSURI NO KAISETSU, *Farumashia*, **28** (1), 52-55 (1992).
- 8) T. Nishimura, N. Murakami, N. Yokura, M. Shinguu, Y. Nozu, S. Sakai, *J. Jpn Soc. Hosp. Pharmac.*, **37** (5), 35-37 (2001).
- 9) Y. Kato, K. Matsumoto, M. Ohkuma, H. Sunada, A study of rapidly disintegrating tablets prepared by the surface modifying method, *J. Pharm. Sci. Technol., Jpn.*, **61** (3), 109-118 (2001).
- 10) Y. Bi, H. Sunada, Y. Yonezawa, A. Otsuka, K. Danjo, K. Iida, Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity, *Chem. Pharm. Bull.*, **44** (11), 2121-2127 (1996).
- 11) N. Hoshi, Pharmaceutical excipients-Properties and applications of disintegrating agents-, *J. Jpn. Soc. Pharmaceut. Mach. Eng.*, **7** (2), 23-30 (1998).